REMARKS

Claims 1-40, 46, 48, 50, and 58-73 are pending in this application. The Examiner has withdrawn claims 9, 10, 15-40, and 46, 48, 50, and 58-63. Applicants have amended claims 1-8, 14, and 25-40 and have added claims 64-73. Applicants have canceled claims 41-45, 47, 49, and 51-57 without prejudice or disclaimer.

Restriction Requirement

Applicants thank the Examiner for the courtesy of a telephonic interview on April 8, 2005. In that interview, the Examiner maintained the restriction requirement and elaborated on her position with respect to the grounds for maintaining the restriction requirement.

Applicants reserve the right to petition for withdrawal of one or more of the restrictions, and again respectfully urge the Examiner to rejoin claims, particularly if and when the claims currently under examination are identified as allowable, and to examine any linking claims as appropriate.

The Office Action lists claim 14 as currently pending and under examination. Applicants understand that claims in Group V (including linking claim 14) will be rejoined with Group I if claim 14 is identified as allowable.

35 U.S.C. § 102

The Office Action alleges that claims 1, 5-8, and 14 are anticipated by Yousif et al. (*APMIS* 102:891-900 (1994)).

Specifically, the Office Action at page 5 states:

> **Yousif at page 81, col.2, Materials and Methods describes a method of identifying a protein that binds to a target and to human serum albumin comprising contacting a plurality of diverse proteins such as NPtase, protein A, histone f3, avidin and lysozyme with antibodies (Ig) and Human serum albumin ... and then determining the proteins that bind to the Ig and human serum albumin.**

Without conceding the merits of this rejection, claim 1 has been amended to recite that the plurality comprises at least 10^2 diverse proteins. Yousif does not teach identifying one or a

subset of members of a plurality of at least 10^2 diverse proteins comprising a region encoded by degenerate oligonucleotides. Thus, this reference does not teach all of the elements of claim 1, at least as presently amended. Applicants respectfully submit that Yousif does not anticipate claims 1, 5-8, and 14 and request that this rejection be withdrawn.

35 U.S.C. § 103

The Office Action alleges that claims 1-8 and 11-14 are obvious in light of Yousif (above) in view of Sato et al. (*Biotechnol. Prog.* 18:182-192 (2002)) and Burger et al. (*Int. J. Cancer* 92:718-724 (2001)). Applicants respectfully traverse this rejection because, among other deficiencies, there is no motivation to combine these three references.

The Office Action at pages 6-7 states:

> **Yousif does not disclose a phage library of the proteins (claims 3-4), the in vivo half life of the identified member (as recited in claim 2), invariant cys residues (claim 13). However, Sato discloses at page 182, col. 1 the numerous desirable properties of phage display in identifying protein binding target (i.e., ligand). For example, phage display allows one to rapidly screen several billion peptide sequences ... Also, page 185, RESULTS and DISCUSSION section as to the advantages of cyclic peptide over linear peptide. Burger discloses at page 718 the in vivo half-life determination of a compound containing human serum albumin. Its determination will show whether a compound is rapidly and efficiently cleared from a body of a patient.**

Contrary to the allegation in the Office Action, Applicants respectfully submit that the three cited references fail to render the claimed invention obvious. Regarding the requirements of an obviousness rejection, the MPEP § 2143 states:

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings [.]

The motivation to combine the three references cited in the Office Action is completely absent. The claims recite a method of identifying a protein that can bind to a predetermined target and also to a serum albumin. As will be elaborated below, the teachings of the three cited references are not only exceedingly disparate, but the two primary references, in fact, teach away from the method of claim 1.

Yousif teaches the characterization of a cationic bacterial protein, staphylococcal neutral phosphatase (NPtase). The reference teaches that NPtase may have a role in the pathogenesis of post-infectious sequelae, such as glomerulonephritis (page 891). The reference states that NPtase could "represent a pathogenic factor in staphylococcal infections and their sequelae" (page 896) and concludes with a discussion on the role NPtase has in the pathogenesis of bacterial disease. It proposes that NPtase may have a role in a "bacterial strategy to escape and inhibit the host-specific immune response" (page 899). The reference ends by stating, "Molecules with a spectrum of interaction properties, like NPtase, are of interest as this could represent an important general virulence factor for bacteria" (*Id.*). Although Yousif allegedly teaches that NPtase can bind to HSA [human serum albumin] and to immunoglobulin, in this context, the ability to bind to HSA would appear to be associated with a pathogenic property, e.g., causative of post-infectious sequelae such as glomerulonephritis. Thus, a skilled practitioner reading Yousif would, if anything, associate the ability of a protein to bind to HSA with bacterial diseases and post-infectious sequelae, like glomerulonephritis. To avoid such deleterious effects, one reading Yousif might be motivated to identify a protein that does <u>not</u> bind to a serum albumin, but certainly would not be motivated to identify one that does bind to a serum albumin. Accordingly, Yousif would not have motivated a skilled practitioner to combine the three references and arrive at a method which includes identifying a protein that does bind to a serum albumin.

Sato teaches the use of phage display to identify a peptide ligand for use in HSA purification. The purpose of the study is clearly laid out on page 182:

> Because commercial HSA purified from serum from human donors, possible human pathogens must be removed by laborious and costly processes. Moreover, **current HSA affinity purification ... do not yield highly pure** and correctly folded HSA, making more effective purification schemes desirable. We sought a peptide ligand that could be immobilized on a chromatographic support for an improved affinity purification of HSA. (emphasis added)

The goal in Sato is to identify a peptide that can be used to obtain a very pure, contaminant-free, preparation of HSA, since "HSA preparations require a higher degree of purity than other protein

therapeutics" (also on page 182). Thus, a protein that could bind to both HSA and to a second protein would not be useful to the methods or purpose of Sato because the preparation purified with such a protein would be contaminated with the second protein. Its use would not result in the desired very pure, contaminant-free, preparation of HSA. Thus, Sato teaches away because a protein that can bind to more than HSA alone is contrary to Sato's purpose. As stated in MPEP § 2145(X)(D)(2), "It is improper to combine references where the reference teaches away from their combination." For this reason alone, the obviousness rejections in the Office Action that rely on Sato are unfounded.

Finally, nothing in Burger controverts the reasons in Yousif and Sato that teach away from the alleged combination.

The Office Action concludes at pages 6-7:

> **Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to replace the conventional method of Yousif with phage display as taught by Sato for the advantages derived from said phage display. The numerous advantages provided by phage display would motivate one to its use. Also, to determine the half-life of the identified target binding proteins of Yousif would have been obvious as taught by Burger. The motivation is to determine how rapidly or efficiently a compound is cleared from the system.**

Again, Yousif teaches that a protein with the ability to bind both HSA and another protein can cause deleterious effects. Sato teaches the identification of peptides that are specific for a single target and their usefulness in preparing very pure, contaminant-free preparations of the single target protein. Because the goal in Sato is to obtain very pure preparations of a single target protein, the reference teaches away from identifying proteins that can bind to more than one target. Such proteins would have no applicability in the methods of Sato because their use would not result in very pure, contaminant-free preparations of the single target protein. Accordingly, one would not be motivated, as alleged by the Examiner, to "replace the conventional methods of Yousif" with those of Sato because Sato did not seek to identify a protein that binds to HSA and another protein. Likewise, Yousif provides no reason to identify a protein that binds to HSA as such a protein might be linked to glomerulonephritis.

Finally, MPEP § 2143.01 states, "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the

desirability of the combination" (emphasis added) *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). For at least the reasons set forth above, not one of the cited references would have suggested the desirability of the combination of the three references. Thus, Applicants respectfully request that the rejection of claims 1-8 and 11-14 as allegedly obvious in light of Yousif, Sato, and Burger be withdrawn.

The Office Action alleges that claims 1-8 and 11-14 are obvious in light of Yousif (above) in view of Sato et al. (above), Burger et al. (above) and Rouslahti (U.S. Patent No. 6,177,542). The Office Action at page 7 states:

> **Yousif does not disclose the target as integrin. However, Rouslahti discloses at col. 1, lines 25-33 that integrins control many medically important biological phenomena ... Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use integrin as a target in the method of Yousif as taught by Rouslahti. One would have been motivated to determine integrin as a target because of its numerous effects or medical biological phenomena, specifically its effect on cancer cells.**

Applicants have addressed Yousif, Sato, and Burger above. Rouslahti does not cure any of the deficiencies of Yousif, Sato, and Burger to render the claimed invention obvious. Rouslahti does not contain a teaching, suggestion, or motivation to combine the references in a way that would have rendered the claimed invention obvious. Broad language that integrins may control many important biological phenomena cannot be purported to motivate combining four references, particularly where both Yousif and Sato teach away from the combination. Applicants respectfully request that the rejection of claims 1-8 and 11-14 as allegedly obvious in light of Yousif, Sato, Burger, and Rouslahti be withdrawn.

CONCLUSION

Applicants respectfully submit that the rejections to claims 1-8 and 11-14 for lack of novelty and as obvious have been overcome. Applicants respectfully submit that all claims are in condition for allowance. Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do Applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

All amendments and cancellations are made without prejudice and disclaimer and may be made for reasons not explicitly stated or for reasons in addition to ones stated.

Please apply any charges including the charge for multiple dependent claims to deposit account 06-1050, referencing Attorney Docket No. 10280-058001.

Respectfully submitted,

Date: 27 April 2005

Ramon K. Tabtiang
Reg. No. 55,658

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

21068533.doc